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Volume Loss of the Medial Temporal Lobe Structures in Subjective Memory Impairment

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Key Words

Alzheimer's disease · Amygdala · Entorhinal cortex · Hippocampus · Subjective memory impairment

Abstract

Background/Aims: Subjective memory impairment (SMI) has been suggested as a manifestation of Alzheimer's Disease (AD) preceding mild cognitive impairment (MCI). In this study, we determined the volumes of the hippocampus, the entorhinal cortex (EC) and the amygdala to provide biological evidence for AD in SMI. **Methods:** Regional volumetric measures were manually traced on 3-Tesla MRI scans. **Results:** Total brain volume did not differ between the groups. Individuals with SMI had reduced volumes of the hippocampus bilaterally (right $p = 0.001$; left $p < 0.001$), the bilateral EC (right $p = 0.031$, left $p = 0.006$) and the right amygdala ($p = 0.01$) compared to the control group. **Conclusion:** Volume reduction of bilateral hippocampus, bilateral EC and right amygdala supports the concept of SMI as a very early manifestation of AD prior to MCI. SMI may indicate awareness of a degenerative process that can still be functionally compensated.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the central nervous system that is characterized by impairment of memory, language and thought [1]. Dementia is diagnosed when these clinical symptoms interfere significantly with social functioning and activities of daily living. At this point, considerable and irreversible neuronal damage has already occurred. Landmark neuropathological findings include selective neuronal and synaptic losses [2], extracellular neuritic plaques and neurofibrillary tangles. The earliest neuropathological changes originate in the medial temporal lobe, including the hippocampus, the entorhinal cortex (EC) and the amygdala [3–5]. There is an increasing interest in the identification of patients in the earliest stage of AD, prior to clinical manifestation of dementia, in order to provide effective early intervention that aims at delaying significant impairment [6, 7].

It has been shown consistently that mild cognitive impairment (MCI) is a prodementia syndrome [8]. MCI is defined as objective cognitive decline with intact activities of daily living [9]. Several studies have demonstrated that MCI patients are at higher risk of developing AD, with an estimated conversion rate of 10–15% per year, compared to 1–2% per year in the cognitively healthy el-

Table 1. Sample description

	SMI (n = 21)	Controls (n = 48)	Difference
Age, years	66.3 ± 6.15	65.8 ± 7.22	T = 0.29 p = 0.774
Male/female	15/6	31/17	$\chi^2 = 0.308$ p = 0.579
Years of education	14.6 ± 3.57	15.1 ± 2.8	T = -0.65 p = 0.515
BDI	6.2 ± 4.8	2.75 ± 2.8	T = 3.77 p < 0.001*
ApoE (4+/4-)	5/16	11/37	$\chi^2 = -0.001$, p = 0.971

* Significant differences compared with the control group.

derly [8, 10]. In patients with MCI, neuropathology studies have reproducibly detected neuronal loss in medial temporal lobe structures, including the hippocampus, EC and amygdala [11, 12]. Consistent with these findings, several structural brain MRI studies reported smaller volumes of the hippocampus, the EC and the amygdala in patients with MCI compared with unimpaired elderly [13–15]. It has been suggested that atrophy of medial temporal lobe structures predict progression from MCI to AD [16, 17].

Neuropathological features of AD, however, are present even years prior to clinical manifestation of MCI [18]. Since cognitive impairment develops slowly, it has been suggested that subjective memory impairment (SMI) may precede MCI in the clinical manifestation of AD [19, 20]. SMI is defined by the mere subjective feeling of memory decline, but – in contrast to MCI – persons with SMI perform within the normal range on standard neuropsychological tests. The concept of SMI as a precursor of AD is supported by the majority of longitudinal studies in large cohorts that identified SMI as a predictor of dementia [21, 22].

In a pilot MRI study, we found a reduction of the EC volume in SMI subjects as compared with controls who did not complain of impairment, providing evidence of AD-related neurodegeneration [22]. Total hippocampal volume was not reduced in that sample; however, 3-dimensional surface analysis revealed a localized volume reduction [23]. Other studies with limited sample size also failed to identify hippocampal volume reduction in SMI [24]. In larger SMI samples, however, hippocampal volume reduction was observed [25, 26]. The aim of the

present study was threefold: (1) to identify hippocampal volume reduction in a larger and independent SMI sample as compared with our initial study [27]; (2) to replicate the finding of EC volume reduction in SMI, and (3) to additionally measure the volume of the amygdala, as a medial temporal lobe structure that is vulnerable to early AD pathology.

Subjects and Methods

Subjects

All participants with SMI (n = 21) were referrals to the memory clinic of the Department of Psychiatry of the University of Bonn for the diagnostic work-up of memory complaints. We only included subjects with informant confirmation of memory decline. The consensus of self and informant responses increases the validity of reports of memory impairment [28]. The onset of memory impairment had to have been observed within the last 10 years in all subjects. The time criterion was employed to exclude subjects with lifelong memory complaints.

The healthy control subjects (n = 48) without memory complaints were recruited from the general population by advertisement. None reported any significant memory decline or impairment.

The 2 groups did not differ with regard to age, gender or years of education (table 1).

Normal cognitive function in all participants was defined by the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neuropsychological battery [29] for which German age-, gender- and education-adjusted norms are available at www.memoryclinic.ch. All subjects with SMI and all healthy controls scored within 1.5 SD on all subtests of the CERAD battery. The SMI group did not differ from the healthy control group on any CERAD item (table 2). There was, however, a significant difference in the Mini-Mental State Examination (MMSE) between both groups.

All participants underwent the Structured Clinical Interview for DSM-IV to identify current or lifetime psychiatric diagnoses. Subjects with any psychiatric disorder at present or in the past were excluded. Only a single depressive episode more than 10 years ago, which was reported by 2 subjects with SMI and 4 subjects in the control group, was not considered an exclusion criteria. Current (sub-threshold) depressive symptoms were additionally evaluated by the Beck's Depression Inventory (BDI). This self-rating scale contains 21 questions, each answer is scored on a scale value of 0 to 3. A total score greater than 12 indicates a clinically relevant depression.

Additional exclusion criteria for both groups were any significant past or present neurological or medical diseases. Patients with medication that is known to affect brain function were not included.

Apolipoprotein E (ApoE) genotype was determined in all subjects. The groups did not differ with regard to the presence of the ApoE 4 allele (table 1).

All participants gave written informed consent prior to their inclusion in the study. The local ethical committee approved all procedures used in this study.

Table 2. Neuropsychological test scores derived from the CERAD neuropsychological battery

	SMI (n = 21)	Controls (n = 48)	Difference	
			T	p
Mini-mental state examination	28.6 ± 1.2	29.3 ± 1.0	-2.64	0.01
Semantic verbal fluency (1 min)	24.1 ± 5.5	25.7 ± 5.9	-1.08	0.282
Boston naming test (max. 15)	14.8 ± 0.6	14.7 ± 0.5	0.38	0.71
Verbal immediate recall (max. 30)	22.2 ± 3.3	22.8 ± 3.3	-0.66	0.52
Verbal delayed recall (max. 10)	7.9 ± 1.6	8.0 ± 1.5	-0.25	0.68
Verbal recognition (max. 10)	9.8 ± 0.4	9.8 ± 0.6	0.41	0.344
Constructional practice (max. 11)	10.4 ± 1.0	10.7 ± 0.7	-1.53	0.13
Visual recall	10.1 ± 3.1	11.2 ± 2.0	1.72	0.09

Magnetic Resonance Imaging

All magnetic resonance (MR) data were obtained on a 3T MR scanner (Philips Achieva, Philips, Best, The Netherlands), equipped with an 8-channel sense head coil. Four high-resolution T₁-weighted data sets of each participant were acquired consecutively. The sequence parameters were as follows: T₁-weighted 3D Turbo Field Echo (FFE), sense factor 2.5 in the AP direction, 1.5 in the RL direction, TE/TR/Flip = 3.6 msec/7.6 msec/8°, field of view 256 × 256 mm, matrix size 320 × 320, number of slices 170, spatial resolution 0.8 × 0.8 × 0.8 mm. The loss in signal-to-noise ratio due to the high resolution and the application of sensitivity encoding was compensated by acquiring 4 independent data sets which were averaged post hoc after applying a motion correction algorithm as provided by SPM5 (Wellcome Department of Cognitive Neurology, London).

MR Analyses

All volumetric measures were performed by 1 blinded rater (A.W.). The software Analyze 5.0 was used. Prior to the measurement of the target regions, the rater performed a blinded double measure of all regions in 10 subjects. These data were used to calculate the intra-rater variability by means of Pearson correlation coefficient. The total brain volumes were obtained by automated tissue segmentation with SPM5 and adding of grey and white matter tissue probability maps.

Volumetric Measures

Hippocampus

The right and left hippocampi were manually traced on sagittal MR slices, starting on a midsagittal slice throughout the hippocampus. The anterior border was defined by the alveus, which separates the hippocampus from the amygdala. The lateral ventricle served as the posterior border. The fimbria as well as the lateral ventricle and the alveus defined the superior border. Inferiorly the uncus separated the hippocampus from the parahippocampal gyrus. On further medial slices the hippocampus is divided into 2 separate structures by thalamic nuclei. The head of the hippocampus borders the temporal horn of the lateral ventricle from ventral, while the tail borders the same structure dorsally. The intra-rater reliability of the hippocampal volume was $r = 0.98$.

Entorhinal Cortex

The EC protocol was adapted from Insausti et al. [30] and Goncharova et al. [31]. The EC was measured from the level where

the ambiens gyrus, the amygdala and the white matter of the parahippocampal gyrus were first visible to the section preceding the lateral geniculate nucleus. The superior boundary was defined as the sulcus semiannularis and, in more caudal sections, the inferior border of the subiculum. The lateral border was defined as the most inferior medial point of the medial bank of the collateral sulcus. The intra-rater reliability of the EC volume according to this protocol was $r = 0.97$.

Amygdala

The volumes of the amygdalae were defined according to Pruessner et al. [32]. They were manually traced on coronal slices. The posterior end of the amygdala was defined as the point where grey matter first appeared superior to the alveus, lateral of the hippocampus. A horizontal line between the superolateral part of the optic tract and the fundus of the inferior portion of the circular sulcus of the insula was employed as superior border. Defining the tentorial indentation as the inferior border allowed a separation between amygdala and EC. Anteriorly, the border was set by the closure of the lateral sulcus. To define the medial and lateral borders of the amygdala, transverse slices were used. The medial posterior-superior ambient cistern was separated from the amygdala, while further anterior and inferior it had to be distinguished from the EC. Laterally the inferior horn of the lateral ventricle marked the border. The intra-rater reliability of the protocol was $r = 0.98$.

Statistics

The data were analyzed with SPSS for Windows (v. 16.0 in German). To correct for overall brain atrophy, all volumes were divided by whole brain volume.

Univariate analyses of variance (ANOVA) were used to assess group differences of any volumetric measure for each hemisphere separately and for the combined left and right volumes. Sex and ApoE 4 status (carrier/non-carrier) were included as factors. Age, BDI and MMSE were introduced as covariates. Additionally, the interaction of age and amygdala volume was also calculated. Effect sizes d were calculated for each group comparison according to:

$$d = \frac{\text{mean}(X_{\text{Control}}) - \text{mean}(X_{\text{SMI}})}{\sqrt{\text{std}(X_{\text{Control}})^2 + \text{std}(X_{\text{SMI}})^2} / 2}$$

Table 3. Volumetric measures normalized to total brain volume

	Controls	SMI	dF	F	p	Effect size
Total brain volume	1.02 ± 0.09	1.01 ± 0.12	1	0.980	0.756	−0.09
Summed hippocampus (right + left)	4.03 ± 0.55	3.55 ± 0.39	1	14.909	<0.001*	−1.01
Left hippocampus	2.04 ± 0.30	1.80 ± 0.20	1	15.769	0.000*	−0.94
Right hippocampus	2.00 ± 0.27	1.75 ± 0.22	1	11.314	0.001*	−1.02
Summed EC (right + left)	1.03 ± 0.25	0.78 ± 0.19	1	7.304	0.009*	−1.13
Left EC	0.51 ± 0.13	0.37 ± 0.09	1	8.316	0.006*	−1.25
Right EC	0.51 ± 0.14	0.42 ± 0.12	1	4.913	0.031*	−0.69
Summed amygdala (right + left)	2.77 ± 0.38	2.51 ± 0.40	1	5.088	0.028*	−0.67
Left amygdala	1.39 ± 0.21	1.29 ± 0.19	1	2.119	0.151	−0.50
Right amygdala	1.38 ± 0.20	1.22 ± 0.23	1	7.162	0.010*	−0.74

* Significant differences compared with the control group (ANOVA using age, BDI and MMSE as covariates, and sex and presence of ApoE4 as factors).

Results

Brain volume did not differ between both groups. The SMI group had smaller bilateral hippocampi and EC as compared with the control subjects. The right amygdala was also smaller in the SMI group as compared with the controls. The left amygdala volume did not differ between both groups. Table 3 lists the data of all regions. Of all covariates in all analyses, only age was significantly associated with amygdala volume in the whole sample [left amygdala $F = 9.382$, $p = 0.003$; right amygdala $F = 7.678$, $p = 0.008$; summed (right + left) amygdala $F = 10.195$, $p = 0.002$]. There was no association between amygdala volume and age in the SMI subsample. There was an association between the right, left and summed amygdala volume in the control subsample (left amygdala $r = -0.406$, $p = 0.004$; right amygdala $r = -0.445$, $p = 0.002$; summed amygdala $r = 0.462$, $p = 0.001$).

Discussion

We found volume reduction of bilateral hippocampus, the bilateral EC and the right amygdala in subjects with SMI in comparison to control subjects. The 2 groups did not differ with regard to cognitive performance. Variables impacting on brain volumes, such as age, BDI, MMSE, sex and ApoE4 status, were included as covariates. In a pilot study with an independent smaller sample, we did not observe significant volume reduction of the hippocampus in SMI subjects as compared with controls

[27]. One potential reason for this inconsistency is the difference in sample size between the 2 studies. Another explanation could be that the pilot study was performed on a 1.5-T scanner, while in the current study all MR data were obtained on a 3-T MR scanner with a resolution of $0.8 \times 0.8 \times 0.8$ mm as opposed to $1 \times 1 \times 1$ mm, potentially yielding a higher sensitivity. Another reason could be that in the pilot study SMI was defined as self-reported feeling of memory worsening with normal neuropsychological performance. In the present study we additionally included only subjects with informant confirmation of memory decline. The consensus of self and informant responses increases the validity of reports of memory impairment [28]. The significant reduction of the hippocampus in the present study confirms other reports of hippocampal volume reduction in SMI [25, 26]. Hippocampal atrophy has been shown to be one of the most robust and consistently documented findings in mild AD and MCI and can be detected very early in the disease process [33]. At present, there is increasing evidence that hippocampal atrophy can be observed prior to the MCI stage in AD with SMI as the corresponding clinical syndrome. In a large population-based sample Stewart et al. [34] found an association between lower hippocampal volume and subjective memory impairment. But the authors only discriminated between dementia, SMI and non-complaining persons. Individuals with mild neuropsychological deficits might have been included in the SMI group. In our study we only included persons that performed within the normal range on standard neuropsychological tests.

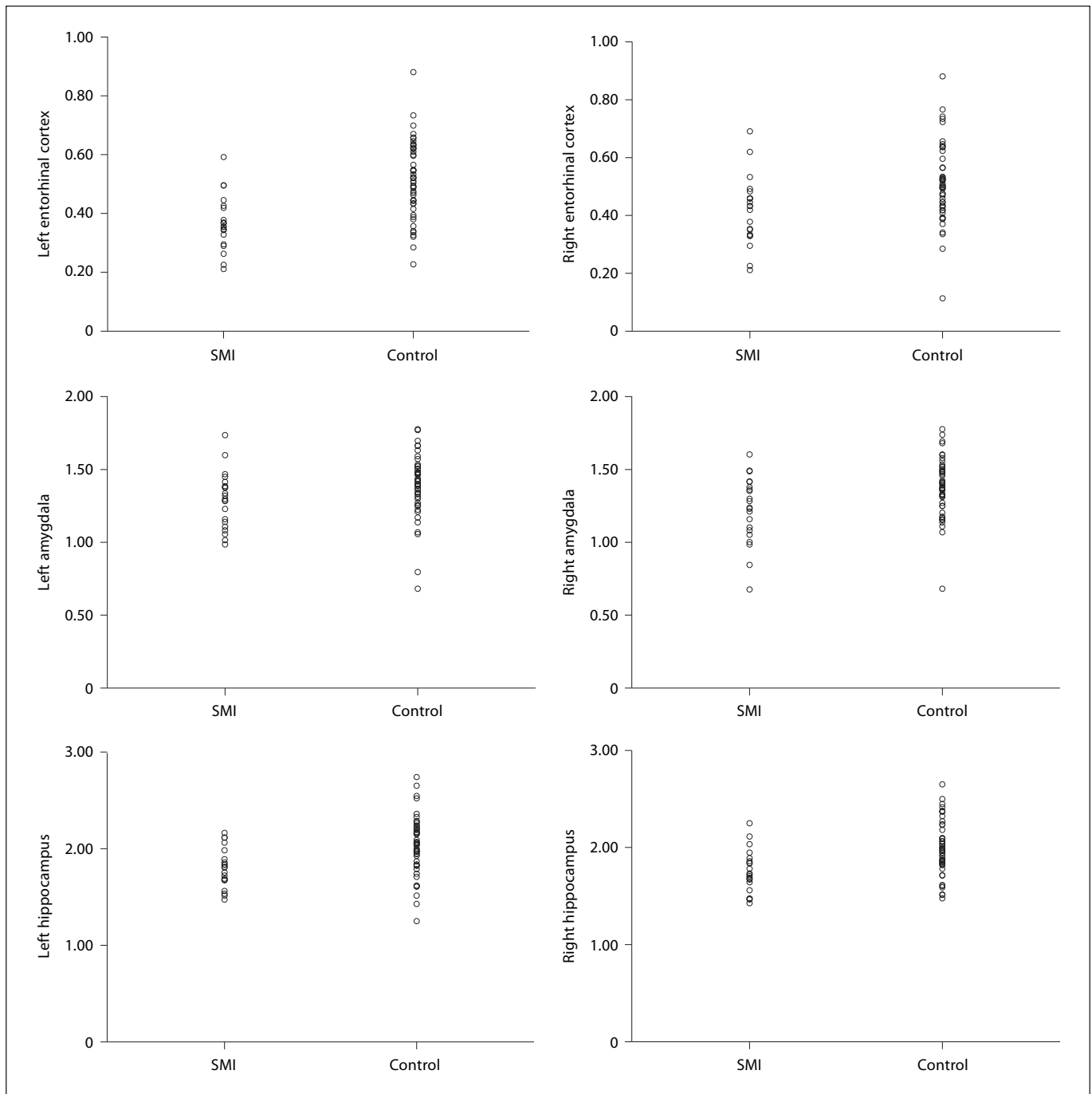


Fig. 1. Left and right volumes of the entorhinal cortex, amygdala, hippocampus normalized to total brain volume.

We replicated our initial finding of EC volume loss in SMI in an independent sample of SMI subjects and controls [27]. In keeping with the literature, EC atrophy has repeatedly been demonstrated in patients with pre-dementia syndromes [35]. Similar to our data, Dickerson et

al. [16] reported a significant volume reduction of the EC and hippocampus in individuals who reported memory decline. The group of memory complainers, however, included both, patients with SMI and MCI. The authors did not differentiate between these 2 subgroups. Killiany et al.

[33] reported that EC atrophy predicts dementia within 3 years and found that the EC is affected earlier than the hippocampus. In our study the effect size of the summed EC volume reduction was slightly greater than the effect size of the summed hippocampal volume reduction, which may indicate more pronounced volume reduction confirming neuropathological models.

As a novel finding we also observed volume reduction of the right amygdala in SMI subjects. The amygdala is less frequently the target of volumetric studies in AD and MCI. However, those studies that assessed amygdala volume, consistently found a reduction in patients with AD compared with healthy elderly individuals [36, 37]. In subjects with MCI, Bottino et al. [38] reported smaller amygdala volumes in comparison with healthy elderly subjects. Accordingly, Petersen et al. [39] found that most patients with MCI met neuropathological criteria for incipient AD up to Braak III stage, including amygdala affection. In a population-based cohort, den Heijer et al. [40] reported prediction of dementia by amygdala and hippocampal atrophy in cognitively healthy subjects [40]. Respectively, Stewart et al. [34] found an association between amygdala atrophy and persons with SMI in their large community sample.

A correlation between amygdala atrophy and aging has consistently been reported. In our study amygdala volume was only negatively associated with age in the control subsample, but not in the SMI subsample. This may be interpreted as an indication of an accelerated amygdala volume reduction in the SMI group obscuring normal effects of aging.

With regard to degree of atrophy expressed by effect size, the affection of the EC and the hippocampus is greater than that of the amygdala in our study. This fits the proposed pathological staging scheme in AD. According to the Braak stages neurofibrillary tangles first occur in the EC and hippocampus (transentorhinal stages I and II), before spreading out into the amygdala and basolateral temporal lobe (limbic stage III–IV) [3].

We found differences in atrophy between the left and right hemisphere. While the volume of the right amygdala was smaller in the SMI group compared with the control subjects, the left amygdala was not. By contrast, the effect size of the right EC difference between both groups was smaller than that of the left EC difference. Thus, we did not observe clear laterality effects. This might be attributable to the sample size. However, the literature regarding laterality of volume atrophy in MCI and AD is very heterogeneous without clear evidence of either left or right dominance of atrophy [38].

Our study has limitations. First, this is a cross-sectional investigation. Only longitudinal follow-up will eventually confirm the hypothesis of brain volume atrophy as an indicator of AD in SMI. However, observation periods of many years are needed to identify reliably who will eventually suffer from dementia [19, 20].

A potential confound is the slightly higher score on the depression self-rating scale (BDI) in the SMI group. However, neither the SMI subjects nor the healthy controls had a clinically relevant depression or fulfilled DSM IV criteria for a major depressive episode. Still, we accounted for this potential confound by including the BDI score as a covariate in all analyses. We did not find an association of any measure with the BDI score. Also, higher BDI score in the SMI group may not necessarily reflect sub-threshold depressive symptoms, but may be related to differences in self-awareness due to specific personality traits, which have been found to be more prevalent in SMI subjects [41]. In this study, we did not assess these variables in detail.

Another limitation in terms of the generalizability is the memory clinic based origin of our sample, with most participants having high levels of education and superior pre-morbid cognitive performance, which may modulate effects of brain pathology on cognition [35]. However, our data are in agreement with findings from population-based studies [26].

Finally, SMI as a category is not yet fully established and there is no standard definition. Also, mediotemporal lobe atrophy is not specific for early AD as it occurs also in other neurodegenerative disorders. This has to be considered when comparing these data with other studies.

In conclusion, in SMI subjects we observed structural brain changes that are similar to those seen in MCI and mild AD. We replicated hippocampus and EC volume reduction and extended these findings to reduction of the right amygdala volume. These results further support the model of SMI as an early clinical correlate of AD pathology. Subjective cognitive failures may indicate the awareness of very mild early impairment that is still compensated.

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